REMARKS

Claims 1-37, 77, 83-94, 97-108, 119, 121, and 123 are pending in the application. No claims are amended in the present reply. Claims 1-37, 77, 84-87, 93, 94, 97 and 101-108 are withdrawn. Claims 38-76, 78-82, 96, 109-118, 120, 122, and 124-130 were previously cancelled.

The Examiner is requested to reconsider and withdraw the rejections in view of the amendments and remarks contained herein.

TELEPHONIC INTERVIEW WITH EXAMINER

Applicant's representative William A. Ziehler wishes to thank Examiner Lynn A. Bristol for the courtesy, dialogue, and time invested in the telephonic interview conducted on March 21, 2011. The interview provided the chance to further describe features and benefits of the present invention as compared to the art of record. The Examiner appeared to acknowledge that *Herman* and *Slavin-Chiorini* have opposite motivations with respect to half-life and clearance. However, the Examiner also noted that *Slavin-Chiorini* mentions two additional effects with respect to removing a C_H2 domain – more rapid tumor targeting and lack of metabolic uptake in normal tissues. As one proposed example to distinguish the claims from the cited documents, it was suggested by the Examiner that functional language regarding decreasing the clearance rate may serve to differentiate the claims. Although no agreement was reached regarding the present rejections, Applicant's representative appreciates the discussion regarding the pending claims in view of the *Herman* and *Slavin-Chiorini* documents. As such, it is believed that the remarks submitted in the present reply illustrate the patentability of the present claims and effectively address the Examiner's concerns.

REJECTION UNDER 35 U.S.C. § 103 – *HERMAN & SLAVIN-CHIORINI*

Claims 83, 88-92, 98-100, 119, and 121-123 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Herman (U.S. Pub. No. 2005/0069549, published March 31, 2005, filed January 14, 2003; cited in the PTO 892 form of 11/7/2006; hereinafter "*Herman*") in view of Slavin-Chiorini et al. (Int. J. Can. 53:97-103(1993); hereinafter "*Slavin-Chiorini*"). This rejection is respectfully traversed.

During the interview (as noted in the preceding section) the Examiner appreciated that *Herman* and *Slavin-Chiorini* present incompatible goals when it comes to the question of serum half-lives – one of the most important aspects of immunotherapy relates to prolonging half-life and one of the most important aspects of immunodiagnostics relates to a high clearance rate (to reduce radionuclide exposure and a HAMA response), where half-life and clearance rate are inversely related. However, the Examiner noted this is but one of three aspects related to C_H2-deprived antibodies, where disclosed in *Slavin-Chiorini*: "faster clearance rate, more rapid tumor targeting and lack of metabolic uptake in normal tissues demonstrated with the iodine-lableled C_H2 domain deleted cMAb may be an advantage for certain clinical protocols" (p. 102, col. 2, ¶ 3).

Applicants present the following remarks in response to the Examiner's concerns.

First, the low serum half-life in *Slavin-Chiorini* teaches against the use of C_H2-free antibodies as a modification of *Herman's* constructs – this view is also supported by the half-lives reported in *Slavin-Chiorini* on page 102, left-hand column, third paragraph ($T_{½\beta}$ = 7.8 hours is indicated as a "fast plasma clearance rate"). Further, the advantage for certain "clinical protocols," as taught in *Slavin-Choirini*, appear to be for diagnostic clinical protocols, since

nothing else is mentioned, and since the diagnostics discussed in *Slavin-Chiorini* clearly are clinical. The rejection has therefore not reconciled the noted incompatibility of *Herman* and *Slavin-Chiorini*.

In particular, a skilled artisan would not be motivated to combine these documents unless there was some way to overcome the expected faster clearance rate and its recognized negative impact on immunotherapy applications. And no means to do so is provided in the rejection. For a finding of obviousness based on a combination of documents, there must be an apparent reason for a skilled artisan to make the alleged combination. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418, 82 USPQ2d 1385, 1396 (2007) (obviousness includes determining whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue). Moreover, when formulating a *prima facie* case of obviousness, a reasonable expectation or predictability of success is required, as noted in MPEP § 2143.02 and in *KSR v. Teleflex*, *supra*: "The mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art" (emphasis added). That is, there is not a predictable improvement for an immunotherapy application when the antibody-like molecule based on the combination of *Herman* and *Slavin-Chiorini* is now faced with the problem of an increased clearance rate. For example, on one hand, the increased clearance rate may partially offset any increase in tumor targeting or any reduction of metabolic uptake, and on the other hand, the increased clearance rate might wholly obviate any increase in tumor targeting and reduction in metabolic uptake and consequently make the immunotherapy less effective overall. Simply put, it is not predictable that an immunotherapy based on the targeted ligand provided by *Herman* would actually benefit by

making a C_H2-deprived antibody, as per *Slavin-Chiorini*. These documents therefore cannot establish a case of obviousness.

Second, *Slavin-Chiorini* emphasizes that even for diagnostic use, the C_H2-free antibodies tested have weaknesses in that they exhibit lower tumor binding than intact antibodies. This must in Applicant's opinion teach directly against combination with *Herman* since low affinity generally is regarded as an undesirable feature when one discusses therapeutic antibodies. *Slavin-Chiorini* also explicitly states that further clinical testing is required, which must mean that nothing can be concluded in respect of the usefulness of the C_H2-free antibodies, even for clinical diagnostic purposes. In view of this, it appears very far-fetched that the skilled person would readily attempt to use such antibodies in order to modify the multispecific ligands taught in *Herman*.

Third, *Slavin-Chiorini* expresses other doubts as to the usefulness of the C_H2-free antibodies: see for instance page 102, right-hand column, lines 9-12 (studies of metabolic uptake necessary when using other radionuclides), and lines 24-28 (the C_H2-domain free constructs differ in their chain assembly and comparative studies are necessary).

Fourth, the results from Fredriksen et al. 2006 (a copy is enclosed; cited by Examiner 04-10-2008) show that vaccibodies are present in serum after 5 months from one single DNA immunization, *cf.* the paragraph bridging pages 2 and 3 (170 days > 5 months). This must mean that the vaccibody encoding construct is extremely effective and/or that vaccibodies have a surprisingly long serum half-life (when compared to *Slavin-Chiorini's* 7.8 hours). That is, it generally takes about 5 half-lives to effectively remove a drug from circulation after the last administration, meaning that it would take less than 2 days (5 times 7.8 hours is 1.6 days) for *Slavin-Chiorini's* antibody to be out of circulation. If one uses that information in this case, one

can only conclude that the expression plasmid administered was still active up to 1 day before the 5 month date and/or that the half-life of the encoded vaccibody is considerably longer than 7.8 hours. It does not seem that this could be expected from the cited prior art. In order to obtain a high serum concentration of a drug having a low serum half-life, the daily dosage has to be high – in the context of a DNA vaccine that would require a very high expression rate.

Fifth, the vaccibody encoding constructs of the present invention appear to provide for expression of superior immunogens, so the constructs provide for improved DNA vaccination – based on the findings in Fredriksen and Bogen 2007 (a copy is enclosed; cited by Examiner 04-10-2008) the improvement appears to be the consequence of dimerization of the encoded protein and the improvement in fact provides a surprising immunogenicity which is higher than the immunogenicity of the administered proteins themselves. These advantages of the claimed constructs could not be expected from the prior art.

Sixth, it is also important to once again point out that the Examiner has not pin-pointed one single embodiment in *Herman*, which, if one combined it with the teaching of *Slavin-Chiorini*, would read on the presently claimed subject matter.

To summarize, it appears to be fair to state that *Slavin-Chiorini* is a document which does not demonstrate results that are in any way conclusive or predictable – two things teach directly against combination with *Herman*, namely the low serum half-life reported for C_H2-free antibodies but also the reported low degree of binding to the intended tumor target. The features that in the Examiner's opinion provide an incentive for the skilled artisan to combine into *Herman* are, first of all, primarily relevant in diagnostic settings using radionuclides, but *Slavin-Chiorini* actually expresses serious doubts as to the general applicability of the C_H2-free

antibodies and suggests that further testing should be done in respect of both metabolic uptake and antibody assembly.

So, the rejection's suggested combination does not satisfy the criteria set forth in e.g. *KSR v. Teleflex*, since *Slavin-Chiorini's* technology has not been demonstrated to successfully modify antibodies in a manner which can be regarded as predictable – this is evidenced by *Slavin-Chiorini's* own remarks. And, when considering that the nucleic acids of the application do in fact provide surprising and unexpected advantages when used in DNA vaccination, the present claims are not obvious over the prior art for this additional reason.

Reconsideration of the claims and withdrawal of the rejection are respectfully requested.

CONCLUSION

It is believed that all of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the Examiner reconsider and withdraw all presently outstanding rejections. It is believed that a full and complete response has been made to the outstanding Office Action and the present application is in condition for allowance. Thus, prompt and favorable consideration of this amendment is respectfully requested. If the Examiner believes that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (248) 641-1600.

Respectfully submitted,

Dated: April 14, 2011

By: _____

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enclosures: Fredriksen et al. 2006 (10 pages)
Fredriksen and Bogen 2007 (9 pages)

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